## REMARKS

Claims 1-14 are pending in the application and were subject to examination. Claims 1, 6-8, and 14 were rejected under 35 U.S.C. § 112, second paragraph; claim 14 was rejected under 35 U.S.C. § 101; claims 1-14 were rejected under 35 U.S.C. § 112, first paragraph; claims 10-12 were rejected under the judicially-created Doctrine of Obviousness-type double patenting; claims 1 and 9-13 were rejected under 35 U.S.C. § 102(e); and claims 1-13 were rejected under 35 U.S.C. § 103(a). Each of the rejections is addressed below.

First, Applicants note that the specification has been objected to, on the basis that page 1 does not include a page number. This objection has been met by the present amendment to page 1, by which a page number is added. Also, making reference to M.P.E.P. § 608.01(b), the Examiner has objected to the abstract for missing the application number. Applicants' review of this M.P.E.P. section did not reveal a requirement for including application numbers on abstract pages. Applicants thus request clarification as to this requirement and, in particular, information as to where on the abstract page the application number is to be inserted.

Applicants also note that new dependent claims 15-44 have been added to the application. Support for these new dependent claims is as follows. Claim 15 is supported, for example, on page 2, lines 14-21, and on page 5, where details of the construction of viruses of the invention are described. Claims 16-22 are supported by original claims 2-9; claims 23-29 are supported by original claims 2-8 and 10; claims 30-36 are supported by original claims 2-8 and 13; and claims 37-44 are supported by original claims 2-9 and at page 4, lines 9-26 of the specification. No new matter has been added by the present amendments.

Rejections under 35 U.S.C. § 112, second paragraph

Claim 1 was rejected under § 112, second paragraph for indefiniteness, on the basis that it is not clear whether the attenuating mutation specified in the claim is present in the pre-membrane or envelope sequences, or whether it may be in either of these sequences. In response, Applicants note that claim 1 now specifies that the mutation(s) of the claim is/are within the envelope protein. Applicants thus request that this rejection be withdrawn.

Claims 6-8 were rejected under § 112, second paragraph for indefiniteness, on the basis that is not clear whether "conservative amino acid thereof" refers to the first or second amino acid specified in each of these claims. In response to this rejection, claims 6-8 have each been amended herein to specify a particular amino acid of which a conservative substitution can be made.

Claim 14 was rejected under § 112, second paragraph for specifying a use without providing any steps involved in the method/process. This rejection can now be withdrawn, as claim 14 has been canceled.

Rejection under 35 U.S.C. § 101

Claim 14 was rejected under § 101 for reciting a use, without any steps involved in the process. As is noted above, claim 14 has been canceled, rendering this rejection moot.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 1-14 were rejected under § 112, first paragraph for lack of enablement, on the basis that the recitation of "an attenuating mutation" is too broad. In response, and in the interest

of expediting prosecution, Applicants have amended the claims herein to specify particular regions in which the attenuating mutations of the claims can be present: amino acids 102-112, amino acids 311-321, and amino acids 435-445. Support for this amendment can be found on page 3, lines 26 and 27 of the application as filed.

Each of the small regions now specified in claim 1 encompasses specific mutations that were described in the experimental examples of the application and shown to have effects on neurovirulence, alone and in combination (see, e.g., Tables 4 and 5 of the application). Thus, the claims now focus on exemplified mutations, as well as mutations in sequences in the regions of the exemplified mutations. Any testing of mutations in these regions certainly would not require undue experimentation. Further, because the regions include amino acids found by the present Applicants to affect virus neurovirulence properties, it can reasonably be expected that other effective mutations can be found in these regions, without undue experimentation. Applicants thus submit that the present claims are enabled, and that this rejection should therefore be withdrawn.

Applicants further note with respect to the rejection under § 112, first paragraph that the Examiner stated on page 4 of the Office Action that the specification enables "a chimeric virus comprising an attenuated Yellow Fever virus backbone encoding a West Nile pre-membrane and envelope proteins comprising multiple locations or single locations at position 107." In view of this statement, Applicants request reconsideration of the rejection as it pertains to claims specifying such mutations (e.g., claims 3-6 and the corresponding new dependent claims (i.e., claims 17-20, 24-27, 31-34, and 39-42)), even without consideration of the present amendments and arguments set forth above. In addition, Applicants submit that the specification supports not

only a single mutation at position 107, but also single mutations at positions 316 and 440 as well. In particular, data obtained with viruses including such single mutations is provided in Table 5 of the application.

In view of the above, Applicants respectfully request that the rejection under § 112, first paragraph be withdrawn.

Double Patenting Rejection

Claims 10-12 were rejected under the judicially-created Doctrine of Obviousness-type double patenting over claims 1, 8, and 9 of U.S. Patent No. 6,878,372. As is noted above, the present claims now specify the presence of one or more mutations in particular regions of the West Nile virus envelope protein. Such mutations are not described or suggested in the '372 patent. Applicants thus request that this rejection be withdrawn.

Rejection under 35 U.S.C. § 102(e)

Claims 1 and 9-13 were rejected under § 102(e) as being anticipated by U.S. Patent No. 6,696,281. As is noted above, the claims now specify the presence of one or more mutations in particular regions of the West Nile virus envelope protein. Such mutations are not described or suggested in the '281 patent. Applicants thus request that this rejection be withdrawn.

Rejection under 35 U.S.C. § 103(a)

Claims 1-13 were rejected under § 103(a) for obviousness over Guirakhoo et al., Virology 257:363-372, 1999; Poidinger et al., Virology 218:417-421, 1996; Yang et al., J. Inf. Dis.

184:809-816, 2001; and Allison et al., J. Virol. 75:4268-4275, 2001. Applicants respectfully request that this rejection be withdrawn.

The Guirakhoo paper is cited for teaching that Yellow Fever virus can be used as a backbone to deliver flavivirus genes, such as pre-membrane and envelope genes of Japanese encephalitis virus; Poidinger is cited for teaching that West Nile virus is a close relative of Japanese encephalitis virus; Yang is cited for teaching that West Nile virus antigens can be used to induce an immune response; and Allison is cited for teaching a flavivirus envelope mutation in position 107. Based on these references, the Examiner concludes that those of skill in the art would have been motivated to combine the Yellow Fever virus backbone of Guirakhoo and the West Nile virus protein of Yang, in light of the teachings of Poidinger, to induce an immune response against West Nile virus. The Examiner further states that Allison provides motivation to include in such viruses a mutation in position 107.

Applicants first note that none of the cited references describes or suggests a mutation in regions comprising amino acids 311-321 or amino acids 435-445, as is specified in claims 4, 5, 7, and 8, and the corresponding new dependent claims (i.e., claims 18, 19, 21, 22, 25, 26, 28, 29, 32, 33, 35, 36, 40, 41, 43, and 44). Thus, Applicants submit that this rejection should certainly be withdrawn with respect to these claims. As to claims covering nucleic acid molecules or corresponding viruses including only the mutation described in the cited Allison reference, position 107, Applicants submit the following.

The mutation described in the Allison reference cited by the Examiner, in position 107 of the envelope protein, is described in the reference in the context of tick-borne encephalitis virus (TBE), which, although in the same genus of viruses as West Nile virus (flaviviruses), is a

distinct virus. Also, this mutation is described in the Allison paper in the context of an intact TBE virus, and not in a chimeric flavivirus as in the present case, which does not include any TBE sequences. Further, there is no indication in the Allison reference as to whether any viruses including this mutation would replicate at levels that would be sufficient to induce an immune response (as in the live, attenuated viruses of the present invention) or if they would replicate too much, leading to adverse effects. Thus, the Allison reference does not provide a basis for a reasonable expectation of success in making an effective vaccine by including the mutation they describe in any vaccine strain, not to mention a chimeric flavivirus, such as a chimeric flavivirus including Yellow Fever virus and West Nile virus sequences as in the present claims.

None of the other references provides this information as well. Guirakhoo, for example, describes studies of a chimeric flavivirus including Yellow Fever virus and Japanese encephalitis virus sequences, and not West Nile virus sequences, as in the present claims. Poidinger describes a study of the relatedness of different flavivirus family members, including Japanese encephalitis virus and West Nile virus (both mosquito-borne viruses), but provides no basis for concluding that a mutation such as that described in the Allison paper (for a tick-borne virus) would be effective in the production of a vaccine virus strain for any flavivirus, not to mention that of the present claims. Allison mentions in his paper that 2 wild type viruses; one tick-borne virus Powassan (ref 30 of Allison paper) and one mosquito-borne virus dengue, strain PUO-280 (ref 6 of Allison Paper), also contain the same F (phenylalanine) amino acid as in the presently claimed invention, at residue 107. Nevertheless both Powassan and PUO-280 viruses are wild type viruses and cause disease in humans. From the data provided in Allison' paper, it would not have been obvious that one can make an attenuated virus (chimeric or non-chimeric) to be used

as a vaccine virus for any flaviviruses, not to mention WNV, described in our current invention. Rather, as Allison teaches that the two cited wild type viruses include phenylalanine at position 107, the reference can be viewed as teaching away from including this amino acid at position 107, in an effort to obtain attenuation, as in the present invention. Further, Yang describes a DNA vaccine based on West Nile capsid protein sequences. Not only does the present invention not pertain to DNA vaccines, it also does not involve the use of West Nile capsid protein sequences. Rather, as is specified in claim 1, the capsid sequences in the nucleic acid molecules and viruses of the present invention are derived from Yellow Fever virus.

Thus, as none of the cited references, alone or in combination, provides any suggestion or expectation of success in the use of a mutation in position 107 (or any other position) in a chimeric flavivirus including Yellow Fever virus and West Nile virus sequences, as in the present claims, Applicants respectfully request that this rejection be withdrawn.

## CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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